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EXAMINER
SAIDHA, TEKCHAND

ART UNIT	PAPER NUMBER
1652	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No. 09/673198	Applicant(s) Hashimoto et al.
	Examiner T. Saidha	Group Art Unit 1652 — 9

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 4/2/03 (Election).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-22 is/are pending in the application.

Of the above claim(s) 1-5 and 8-22 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 6-7 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Acti n Summary

DETAILED ACTION

1. ***Election***

Applicant's election with traverse of Group VIII, claims 6-7 in Paper No. 8 [response filed 4.2.03] is acknowledged. The traversal is on the ground(s) that there is a **unity of invention** with respect to claims 1-9 & 12 (in-part) and do have a common technical feature of elevating the productivity of isoprenoid compounds through a DNA encoding an enzyme in the non-mevalonate pathway. In considering an entire pathway involving a series of enzyme every enzyme in the pathway may contribute towards the final product. The argument is considered and found not persuasive because the manner of claiming a particular enzyme which is selected from a group defines how the lack of unity of invention is made. In the instant case the claims are directed to any process involving any of the pathway enzyme(s), therefore, involves distinct enzymes, each having its own distinct functionality, therefore the lack of unity of invention in proper. Further, the Applicants argue that Groups V and VIII have common technical feature of elevating the production of isoprenoid compounds using a DNA encoding a protein having activity to catalyze 1-deoxy-D-xylulose 5 phosphate to produce 2-C-methyl-D-erythritol 4-phosphate [enzyme involved is : 1-deoxy-D-xylulose 5 phosphate reductoisomerase]. Applicants further explain that both the DNA of SEQ ID NO : 31 (Group VIII) and the DNA (*E. coli* yaeM) of SEQ ID NO : 10 (Group V) have a common feature of complementing methyl erythritol-requiring nature of *E. coli* mutant ME7. In response, SEQ ID NO : 31 (Group VIII) and SEQ ID NO : 10 (Group V), though using DNA encoding an enzyme having 1-deoxy-D-xylulose 5 phosphate reductoisomerase activity, but are distinct because the two

sequences are from 2 distinct sources of Rhodobacter (SEQ ID NO : 31) and *E. coli* (SEQ ID NO : 5), have patentably distinct structures and encode varying enzyme activity levels.

Comparing the amino acid sequence homology between SEQ ID NO : 30 and 5, Applicants refer to page 36, line 29 to page 37, line 2, and conclude that the sequence homology between the two sequences is extremely high.

Applicants' reference to the specification do not indicate the level (%) of sequence homology between the sequences. However, an amino acid sequence search and comparison between Applicants' SEQ ID NO : 30 and SEQ ID NO : 5, it was found that the 2 sequences have a sequence homology of 36.1%. However, A DNA sequence search of Applicants' SEQ ID NO : 31 [in the internal database] did not retrieve any hit with Applicants' SEQ ID NO : 10 for the first set of 30 results, indicating that the two DNA sequences have less than 10% homology amongst them. This determination is based upon the search results. Such low levels of homology cannot by standard be classified as extremely high.

Thus, there is no unity of invention among the various groups as indicated before, as well as between Group V and VIII. The United Sates Patent and Trademark Office is not bound by the lack of unity determination by another International Searching Authority. MPEP 1875 states that whether or not the question of unity of invention has been raised by the International Searching Authority, it may be considered by the examiner when serving as an authorized officer of the International Preliminary Examining Authority. Thus, the Examiner is not bound by any previous determination made. In addition, 37 C.F.R. 1.484 indicates that the international preliminary examination is a non-

binding opinion. Finally, 37 C.F.R. 1.499 states that, if the Examiner finds that a national stage application lacks unity of invention under 37 C.F.R. 1.475, the Examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted. Thus, the determination of lack of unity is proper under the PCT treaty.

The lack of unity determination is still deemed proper and is therefore made FINAL.

2. Claims 6-7 (In-part), drawn to a process of producing isoprenoid compound integrating DNA into a vector, wherein the DNA (SEQ ID NO : 31) encodes an enzyme of SEQ ID NO : 30, are pending and under consideration in this examination.

3. ***Priority***

Acknowledgment is made of applicants' claim for priority based on an application filed in Japan on 4.14.98, 8.5.98 and 2.15.99.

4. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. ***Claim Objections***

Claim 6-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 6-7 depend from a non-elected claim 1. Amending the claim(s) to place the claim(s) in proper dependent form, or rewriting the claim(s) in independent form will overcome this rejection. It is important to include all the method step - including the culturing step and recovering the isoprenoid compound from the culture.

6. ***Claim Rejections - 35 U.S.C. § 112*** (first paragraph)

Enablement

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of producing 2-C-methyl-D-erythritol 4-phosphate [enzyme involved is : 1-deoxy-D-xylulose 5 phosphate reductoisomerase], comprising integrating DNA into vector comprising a DNA sequence of SEQ ID NO : 31 from *Rhodobacter sphaeroides,* encoding a protein of SEQ ID NO : 30 having 1-deoxy-D-xylulose 5 phosphate reductoisomerase activity, does not reasonably provide enablement for a process of producing 2-C-methyl-D-erythritol 4-phosphate by culturing a vector transformed host cell containing modified DNA - encoding a protein with the enzyme activity where one to several amino acid residues are deleted, substituted or added to the amino acid sequence of SEQ ID NO : 30. Such modifications amount to changing the sequence of the original enzyme by any extent or homology as compared to the parent, with the only limitation that the resultant enzyme have 1-deoxy-D-xylulose 5 phosphate reductoisomerase activity (claim 6). Further the encoding DNA hybridize under stringent conditions to a DNA of claim 1(e) or (f) and encode 1-deoxy-D-xylulose 5 phosphate reductoisomerase. Such a hybridization may occur under properly defined conditions wherein the sequence homology among the 2 sequences be at least 90%

homology. No guidance is provided in the instant specification to obtain such DNA molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 6 is so broad as to encompass a process using a transformed host cell comprising a modified DNA to any extent or that capable of hybridizing to DNA of SEQ ID NO: 31 and having 1-deoxy-D-xylulose 5 phosphate reductoisomerase activity. Applicants have neither disclosed nor exemplified any of the several mutants or variants encompassed by the scope of the claims. The specification only discloses 1-deoxy-D-xylulose 5 phosphate reductoisomerase DNA of SEQ ID NO : 31 from *Rhodobacter sphaeroides* not any mutant or variant thereof.

However, beyond the sequence of SEQ ID NO : 31, Applicants have not disclosed any other DNA molecule(s). Applicants have not taught or described the DNA sequence(s) or the encoding polypeptide(s) by any detailed characteristics, such as the motifs or domains or conserved regions of the polypeptide(s) chain; or the active sites of the protein, or regions of the protein structure(s) which are less or more or not tolerant to modifications. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the DNA and the encoded amino acid sequence of SEQ ID NO : 31 & 30

respectively; the encoding activity of 1-deoxy-D-xylulose 5 phosphate reductoisomerase *from Rhodobacter sphaeroides*.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any modifications (deletion, substitution or additions) of SEQ ID NO : 30 as well as hybridize to a DNA encoding SEQ ID NO : 30 or a DNA sequence which is 90% similar (in order to hybridize), because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting 1-deoxy-D-xylulose 5 phosphate reductoisomerase activity; (B) the general tolerance of 1-deoxy-D-xylulose 5 phosphate reductoisomerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any 1-deoxy-D-xylulose 5 phosphate reductoisomerase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. No prior art discloses of record disclose sequences having close homology to sequence(s) of 1-deoxy-D-xylulose 5 phosphate reductoisomerase nor teach or establish

(A).....thru....(D), in a manner sufficient to provide guidance to one skilled in the art to enable the claimed invention.

While guidance is provided for how to make 1-deoxy-D-xylulose 5 phosphate reductoisomerase DNA of SEQ ID NO : 31, and in spite of the fact that the level of a skilled artisan is high, guidance to making or finding 1-deoxy-D-xylulose 5 phosphate reductoisomerase DNA or nucleic acid from any source using the sequence of SEQ ID NO : 31, or the transformants or its use in the recombinant production of 1-deoxy-D-xylulose 5 phosphate reductoisomerase protein enabling the process for making 1-deoxy-D-xylulose 5 phosphate is beyond the scope of the enabling disclosure.

Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including 1-deoxy-D-xylulose 5 phosphate reductoisomerase with enormous number of amino acid modifications of the sequence of SEQ ID NOS: 30. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of 1-deoxy-D-xylulose 5 phosphate reductoisomerase gene(s) for integration into a vector having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme(s) in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

7. No claim is allowed.

8. Claims drawn to specific sequences will be in a better condition for allowance.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T K Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
May 6, 2003